## REMARKS

Claims 1, 7, 8, 11, 13-18, 20, 21, 25, 30-33 and 40 have been amended. Support for the amendments can be found in the Specification as filed, for example, in paragraphs [0069], [0075], [0081], [0083], and [0151] and in the paragraph [0054] of the Substitute Specification of the parent Application No. 09/817,014 which was incorporated by reference in this application. Therefore, no new matter has been introduced by these amendments. Claims 12, 22, 23, 29, 34, 36, 83 and 88 have been cancelled without prejudice. Applicant reserves the right to pursue the subject matter of the cancelled claims in a related application. The following addresses the substance of the Office Action.

**Definiteness**

The Examiner has maintained the rejection of Claims 11, 36 and 81 under 35 U.S.C. §112, second paragraph as being allegedly indefinite. More specifically, Claim 11 was found unclear whether the capture nucleotide sequences comprise a sequence which is between about 100 and 600 bases in length, or whether the target comprises a sequence which is between about 100 and 600 bases. Claim 11 has been amended to clarify that the capture nucleotide sequences comprise a sequence which is between about 100 and 600 bases in length. Claim 36 was found unclear for reciting the term "stopper sequence", which does not have an explanation in the Specification. Claim 36 has been cancelled. Claim 81 was found unclear for lacking antecedent basis for the limitation of "said... sequence of between about 15 and about 40 bases". Claim 1 recites: "each of said single-stranded capture nucleotide sequences comprises a nucleotide sequence of about 5 to about 60 bases". This limitation is further limited in Claim 81 as "said single-stranded capture nucleotide sequences comprise a nucleotide sequence of between about 15 and about 40 bases". Therefore, Claim 81 has exact antecedent basis for this limitation. Therefore, Claims 11 and 81 are definite.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

**Novelty**

The Examiner has rejected Claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39, 40, 44, 45, 55-57, 59-61, 81, 83 and 87 under 35 USC §102(b) as being allegedly unpatentable over Guschin et al., (*Appl. Environ. Microbiol.* 1997 63:2397-2402) as evidenced by Yershov et al. (*PNAS*

*USA* 1996 93:4913-4918), Yerschov et al. (USP 5,770,721), Kulisch (US 2006/0003308A1) and Whitlock (US 2005/0106126A1).

> To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). "Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. ...There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

As discussed in the Inventor's Declaration filed herewith under 37 C.F.R §1.132, the inventors' goal was to find the best standard conditions for identifying a nucleotide sequence. among several homologous sequences with homology higher than 30% against at least four other sequences. The inventors tested the effects of the length of the target molecules, the length of the capture molecules, the presence or absence of a spacer separating the capture molecules from the solid support of the microarray, as well as the length and the type of the spacer on the final combination of high specificity and high sensitivity of the method. The inventors showed that when long double-stranded target nucleotide molecules are hybridized to short capture molecules without a spacer, the assay is quite specific but not at all sensitive (i.e. giving false negative results). When long double-stranded target nucleotide molecules are hybridized to long capture molecules without a spacer, the assay is sensitive but not specific (i.e. giving false positive results).

Moreover, long, double-stranded target molecules cannot ordinarily be used with short capture molecules because the kinetics of hybridization will favor the re-annealing of the two long strands of the target molecule over annealing of one long target strand to the short capture molecule. However, Applicants unexpectedly discovered that full-length, double-stranded target molecules of 100 to 800 bases could be used in an assay with capture molecules that also comprise an oligonucleotide spacer. When such a combination was used, the assay became both sensitive and specific (reducing both the false negative and false positive results). Furthermore, the kinetics of hybridization were sufficient to permit obtaining results in a very short time. Thus, the data presented in the Declaration unambiguously shows that the method as claimed is the most sensitive and specific when the conditions are as follows: long double-stranded target nucleotide molecules (100-800 bases), are hybridized to single-stranded capture molecules having a specific sequence of 5-60 nucleotides and an oligonucleotide spacer of at least 40 bases

in length. Additionally, oligonucleotide spacers were unexpectedly superior to non-nucleotide spacers.

Guschin et al. do not use nor suggest using a polynucleotide spacer, and this reference describes fragmenting the target molecules into 40-base single-stranded sequences before applying the fragments to a microchip. Thus, Guschin fails to disclose the use of the "full-length" target or the "spacer comprising a nucleotide sequence" of the pending claims.

For this reason, Claims 1-8, 11-14, 18, 20, 21, 25-27, 30-33, 39, 40, 44, 45, 55-57, 59-61, 81, and 87 are novel and non-obvious over the cited reference, and their rejection under 35 USC §102(b) should be withdrawn.

**Non-obviousness**

The Examiner has rejected Claims 15 and 16 under 35 U.S.C. §103(a) as being allegedly unpatentable over Guschin et al. (1997). More specifically, these claims were rejected because even though Guschin does not teach the detection of the amplified sequences, in the same chamber as amplification takes place, prior to hybridization, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to ensure the presence of amplified DNA prior to hybridizing it to the array.

> To establish a *prima facie* case of obviousness, the PTO must cite one or more references that provide some suggestion or motivation to modify the references to achieve the claimed invention, provide a reasonable expectation of success to achieve the claimed invention, and finally, the cited art must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

As discussed above, Guschin et al. does not anticipate currently amended Claim 1. Moreover, the claimed invention differs from Guschin in several respects that are entirely unexpected in light of Guschin alon. Therefore Claim 1 and all of the claims that depend from Claim 1 are non-obvious in view of the cited reference.

The Examiner has rejected Claims 17 and 36 under 35 U.S.C. §103(a) as being allegedly unpatentable over Guschin et al as applied to Claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39, 40, 44, 45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Brown (USP 5,807,522). More specifically, the Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to analyze homologous sequences by the method of Guschin using cDNA derived from mRNA after reverse transcription as taught by Brown.

As discussed above, Claims 1-8, 11-14, 18, 23, 25-27, 29-34, 39, 40, 44, 45, 55-57, 59-61, 81, 83 and 87 are novel and non-obvious over the primary reference of Guschin et al. The combination of Guschin et al. and Brown et al. does not render the claimed invention obvious because they do not provide any suggestion or motivation to modify the references to achieve the claimed invention, and do teach or suggest all the claim limitations. Accordingly, withdrawal of the rejection of claim 17 under 35 U.S.C. §103(a) is respectfully requested.

The Examiner has rejected Claims 20, 21, and 88 under 35 U.S.C. §103(a) as being allegedly unpatentable over Guschin et al. as applied to Claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39, 40, 44, 45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Livak et al. (USP 5,723,591). More specifically, the Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the art-recognized functionally equivalent homopolymeric oligonucleotide spacer taught by Livak for the polyacrylamide spacer taught by Guschin for the detection of homologous sequences amplified with a single primer pair, as taught by Guschin and to optimize the length of the oligonucleotide spacer.

Claim 88 has been canceled as superfluous in view of the amendments to Claim 1, which now recites that the nucleic acid spacer is at least 40 bases in length. Claims 20 and 21 have been amended in view of the amendments to Claim 1. As discussed above, claim 1 is novel and non-obvious over the primary reference of Guschin et al. The additional reference fails to cure the primary reference's lack of teaching or suggestion of the characteristics of the method according to the present invention as discussed above. Therefore, Applicant asserts that Claim 1 is non-obvious in view of the cited prior art.

The Examiner has rejected Claims 35, 38, 58 and 84 under 35 U.S.C. §103(a) as being allegedly unpatentable over Guschin et al. as applied to Claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39, 40, 44, 45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Martineau et al. (*Antimicrob. Agents Chemother.* 2000, 44:231-238). More specifically, the Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the multiplex PCR, using primers capable of amplifying 16S rDNA from all bacterial species as well as primers to detect antibiotic resistance genes (as taught by Martineau) with the array method of Guschin in order to achieve simultaneous identification of a bacterial pathogen as well as the antibiotic resistance profile of the pathogen.

The additional reference fails to cure the primary reference's lack of teaching or suggestion of the characteristics of the method according to the present invention as discussed above. Therefore, Applicant asserts that Claims 35, 38, 58 and 84 are non-obvious in view of the cited prior art, and respectfully requests withdrawal of their rejection under 35 U.S.C. §103(a).

The Examiner has rejected Claims 47-54, 86, and 89-94 under 35 U.S.C. §103(a) as being allegedly unpatentable over Guschin et al. as applied to Claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39, 40, 44, 45, 55-57, 59-61, 81, 83 and 87 above, and further in view of: Gingeras (USP 6,228,575) - Claim 47; Boon et al. (USP 6,488,932) - Claim 48; Apple et al. (USP 5,451,512) - Claim 49; Klein et al. (USP 6,255,059) - Claims 50, 51, and 53; Murphy et al. (WO 94/05695) - Claim 52; Waxman et al. (USP 6,207,648) - Claims 54 and 90; Vannuffel et al. (WO 99/16780) - Claim 86; Musser (*Clin. Microbiol. Rev.* 1995, 8:496-514) - Claim 89; Rose et al. (*Nucl. Acid Res.* 1998, 26:1628-1635) - Claims 91 and 93; Apostolidis et al. (*Heredity* 1996, 77:608-618, abstract only) - Claim 92; and Dickinson et al. (US 2002/0102578) - Claim 94. More specifically, the Examiner believes that because these additional references describe specific sequences belonging to a Mycobacteria family, MAGE family, HLA-A family, G gene family, cytochrome P450 isoforms family, dopamine or histamine receptors coupled to the G gene family, FemA gene of staphylococci species family, A gyrase family, sequences belonging to specific animal species or sequences belonging to genetically modified organisms, it would have been obvious to combine these references with the teachings of Guschin et al.

The additional references fail to cure the primary reference's lack of teaching or suggestion of the characteristics of the method according to the present invention as discussed above. Therefore, Applicant asserts that Claims 43, 48-54, 86, and 89-94 are non-obvious in view of the cited prior art, and respectfully requests withdrawal of their rejection under 35 U.S.C. §103(a).

**Double patenting**

The Patent Office rejected a number of claims over various claims of copending Application Nos. 09/817,014 and 10/860,388. With respect to these rejections, Applicants respectfully request that they be permitted to defer the filing of any terminal disclaimer until the rejected claims are otherwise indicated to be in condition for allowance.

## CONCLUSION

In view of the foregoing, Applicants respectfully submit the present application is fully in condition for allowance. If any issues remain that may be addressed by a phone conversation, the Examiner is invited to contact the undersigned at the phone number listed below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: July 31, 2006

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